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November 15, 2003

To: Examiner Traviss C. McIntosh,III FAX: 703 308 4556
Group art unit:1623

Re: Meeting on Monday, November 24, 2003
2:00 pm in Crystal Mall 1 to discuss
Continuation Application of Terri L. Butler et al.

Parent Application Serial Number 09/917,292

In preparation for our meeting, please see attached. The declaration of inventor John A. St. Cyr will be entered in the continuation case when a serial number has been assigned. The claims will be presented. I include also an abstract of a publication relating to this invention. I will bring the manuscript with me, or the reprint if it has been received by then.

I look forward to discussing this case with you and Mr. Wilson. If a phone conversation will be beneficial, I can be reached at the above numbers on Monday and Wednesday and at 763 757 0032 on Tuesday and Thursday.

Sincerely,

Kathleen R. Terry

8 pages, including this cover: 4 pages declaration; 2 pages Abstract of article; one page claims.

S/N PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Terri L. Butler et al.	Examiner:	Traviss C. McIntosh, III
Serial Number:	Not assigned	Group art unit:	1623
Filed:	23 October 2003	Docket:	BP.012US2
Title:	COMPOSITIONS AND METHODS FOR IMPROVING CARDIOVASCULAR FUNCTION		

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA, 22313-1450

I, John A. St. Cyr, hereby declare as follows:

1. I am a joint inventor of the above referenced invention. I have received the following degrees from the University of Minnesota: BA, 1973; BS, 1975; MS, 1977; MD, 1980; Ph.D., 1988. In addition, I completed a residency in General Surgery at the University of Minnesota in 1988 and a residency in Cardiovascular Surgery at the University of Colorado in 1991. Since 1991, I have been an independent consultant in research for various companies, investigating cardiovascular methods and devices, and energy metabolism in general. Since 1995, I have consulted with Bioenergy, Inc., the assignee of this patent application, where I am Medical Director and a minority shareholder.

During the period of my master's studies, I began working in the laboratory of Dr. John E. Foker, investigating the improvement of cardiac function following myocardial bypass. Some of the findings are included in the Foker Patent (4,719,201). I have published approximately 100 scientific papers and abstracts, about 20 of which relate to ATP metabolism. Two of these papers are of record in this case.

2. In the Final Office Action in the parent case, Patent Application Serial Number

09/917,292, mailed July 15, 2003, the Examiner rejected claims 4-7 and 9 under 35 U.S.C.§ 102(b) as being anticipated by Cotter et al. and claims 1-3 and 9 and 16 under U.S.C. § 103 (b) as obvious over Cotter in view of Foker and Wakat. I make this declaration in support of the patentability of the claims in the above-identified continuing application.

3. The Examiner stated that Cotter et al teach the ingestion of eight grams of D-ribose per liter of their composition to improve cardiovascular function. Cotter et al is directed at improving the malnutrition commonly found in congestive heart failure. Cotter does not point to the ingredient ribose as being the effective component of the composition. We have found that two to ten grams of ribose, preferably five grams of ribose, taken one to four times a day, preferably at least two times a day, without the vitamins and proteins of Cotter, are sufficient to improve cardiovascular function. In order to obtain the ribose benefit, the patient would have to ingest eight ounces to two and a half quarts of the Cotter composition each day. The Examiner is asked to take notice that congestive heart patients are often restricted in the volume of liquid they are allowed to consume each day.

I was present and assisted in the research leading to the Foker patent, which is combined with Cotter in the obviousness rejection. Our aim at that time was to replenish the ATP levels of dog hearts which had been subjected to ischemic insult, as in cardiac bypass surgery. Among the methods we attempted were the intravenous, post-operative administrations of adenosine, inosine, Concanavalin A and a blocker of the enzyme adenosine deaminase. Adenine plus ribose was found to be effective. It was subsequently found that ribose alone was sufficient to enhance the replenishment of ATP. It was further noted that the ribose needed to be administered for four to five days or the ATP levels would fall again (Foker, column 7, lines 40-61). After that period, ribose administration could be discontinued and ATP levels remained normal.

During the years since these initial studies, many independent researchers have sought to make the benefits of ribose available to human patients with congestive heart failure, without success despite the ready availability of ribose. For example, Dr. Wolfgang Pliml in Germany gave 15 to 20 grams of ribose at a time to patients for up to three days and found improvement

(see specification, page 12, lines 23 et seq. from the Pliml 1992 reference). We know that so high a dosage cannot be sustained as it almost always causes gastrointestinal distress, which is often severe. We believe that this side effect has prevented the adoption of the Pliml methods. In our study, now ongoing with nearly 1000 patients with congestive heart disease and compromised systolic and diastolic function, we have found that five grams of ribose given orally at least twice a day is effective in improving cardiovascular function. We initially tested a ten gram dosage but do not now recommend the ten gram dosage. Even at the lower dosage of five grams, three woman in the study have reported diarrhea. In general, however, this regimen has been well tolerated with fewer than ten overall adverse reaction reports.

Unlike the dogs in the Foker patent, these patients do not have improvement that persists when ribose is discontinued. I attach here a paper from one of our participating doctors. The patients in this study suffered from severe congestive heart disease (Class 2 and 3) with diastolic dysfunction. By the end of the three week study, diastolic function and other parameters of cardiovascular function had improved. When the patients went off the ribose, their condition deteriorated and they requested additional supplement (personal communication). Therefore, we believe that the administration of ribose should be continuous over the course of the disease.

Preliminary studies showed a benefit of co-administration of a vasodilator, which presumably increases access of ribose to muscle tissue. Early formulations included the vitamins and cofactors claimed in the parent application which the Examiner pointed out were disclosed in Wakat. Since these patients are under close supervision of their physicians, we have found that it is not necessary to include these in the present formulation.

4. I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issue thereon.

By: J. A. St. Cyr Date: 11/13/03
John A. St. Cyr

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D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study

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Abstract

Patients with chronic coronary heart disease often suffer from congestive heart failure (CHF) despite multiple drug therapies. D-Ribose has been shown in animal models to improve cardiac energy metabolism and function following ischaemia. This was a prospective, double blind, randomized, crossover design study, to assess the effect of oral D-ribose supplementation on cardiac hemodynamics and quality of life in 15 patients with chronic coronary artery disease and CHF. The study consisted of two treatment periods of 3 weeks, during which either oral D-ribose or placebo was administered followed by a 1-week wash out period, and then administration of the other supplement. Assessment of myocardial functional parameters by echocardiography, quality of life using the SF-36 questionnaire and functional capacity using cycle ergometer testing was performed. The administration of D-ribose resulted in an enhancement of atrial contribution to left ventricular filling (40±11 vs. 45±9%, P=0.02), a smaller left atrial dimension (54±20 vs. 47±18 ml, P=0.02) and a shortened E wave deceleration (235±64 vs. 196±42, P=0.002) by echocardiography. Further, D-ribose also demonstrated a significant improvement of the patient's quality of life (417±118 vs. 467±128, $P \leq 0.01$). In comparison, placebo did not result in any significant echocardiographic changes or in quality of life. This feasibility study in patients with

coronary artery disease in CHF revealed the beneficial effects of D-ribose by improving diastolic functional parameters and enhancing quality of life.

Author Keywords: Coronary artery disease; Heart failure; Ribose; Quality of life

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Claim 1. A method for improving the cardiovascular function of a subject having reduced cardiovascular function consisting of the administration of two to ten grams of D-ribose one to four times daily to the subject for a period of at least one week.

Claim 2. A composition for improving cardiovascular function of a subject consisting of two to ten grams of D-ribose in combination with an effective amount of a vasodilator to a subject having reduced cardiovascular function for a period of at least one week.

Claim 3. The composition of claim 2 wherein the vasodilator is L-arginine, nitroglycerin, a nitrate, a nitrite, papaverine, isoproterenol, nylidrin, isoxsuprine, nitroprusside, adensoine, xanthine, ethyl alcohol, dipyramide, hydrazlaine, minoxidil or diazoxide.

Claim 4. A method for improving cardiac function in a subject consisting of the administration of any one of the compositions of claims 2 or 3 to the subject one to four times per day for at least one week.

Claim 5. A method for relieving the symptoms of peripheral vascular disease in a subject consisting of the administration of any one of the compositions of claims 2 or 3.